THE FREQUENCY AND SIGNIFICANCE OF INFARCTS OF THE PLACENTA, BASED UPON THE MICROSCOPIC EXAMINATION OF FIVE HUNDRED CONSECUTIVE PLACENTÆ

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THE FREQUENCY AND SIGNIFICANCE OF INFARCTS OF THE PLACENTA, BASED UPON THE MICROSCOPIC EXAMINATION OF 500 CONSECUTIVE PLACENTÆ.

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Any one who has occasion to examine a number of placentæ must be impressed with the frequency with which certain degenerative changes occur, which are designated by many terms, but are generally grouped together as infarcts.

Placental infarcts vary very materially in their appearance, as well as in their situation and size. The most frequent varieties of them we shall describe under the following headings:

I. Small, whitish or yellowish fibrous areas, occurring either on the fœtal or maternal surface of the placenta, which vary in size from areas which are hardly visible to the naked eye to those having a diameter of several centimetres. Such areas rarely attain a thickness of more than a few millimetres, and are sharply marked off from the surrounding placental tissue.

II. On section through the placenta, one frequently sees wedge-shaped or irregularly round areas, which are usually dull white in color and present a striated, fibrinous appearance. They are sharply marked off from the surrounding tissue, which appears to be perfectly normal.

III. More rarely, considerable portions of the placenta are involved in the process, and not infrequently one or more cotyledons are converted into a pale, white, dense, more or less fibrous mass, in which one fails to observe the usual spongy structure of the placenta. In other instances, a large portion of the placenta may be involved in the change, and one-half, and sometimes a greater portion, of its entire substance is occupied by the process.

IV. Not infrequently one observes a broad rim of whitish or yellowish-white material, which extends for a varying distance

around the margin of the fœtal surface of the placenta, taking in a larger or smaller portion of its periphery, and occasionally forming a complete ring around it. These bands vary from a few millimetres to three or four, and sometimes five centimetres in breadth. They lie beneath the amnion and rarely attain a thickness of more than a few millimetres, except at the extreme margin of the placenta, where it merges into the membranes. This condition is known as placenta marginata.

In a certain number of cases, the band of tissue, instead of being situated at the margin of the placenta, lies somewhere between it and the centre of the organ, thus forming a broad zone more or less parallel to its periphery, but separated from it by apparently normal placental tissue. To this condition the term "margo placentæ" is sometimes applied.

V. In rarer instances one finds a larger or smaller portion of the placenta occupied by a pinkish or brickdust-colored mass, irregularly shaped, more or less solid, and sharply marked off from the surrounding tisssues. Such masses vary considerably in size, and occasionally occupy a large portion of the organ. They are usually most marked on the maternal side of the placenta, but not infrequently extend through its entire thickness. To these the term, "red infarcts," is occasionally applied.

Still more rarely one finds scattered through the substance of the placenta, round areas varying from bright red to almost black in color, which are apparently composed almost entirely of blood, and are sharply marked off from the surrounding tissue by a capsule, which presents a more or less fibrous appearance. Such structures differ considerably in size, varying from 1 to $2\frac{1}{2}$ or 3 cm. in diameter. They may occur singly or in considerable numbers, and in rare instances the entire placenta may be studded with them, when it appears markedly nodular on external examination, and on section presents an appearance which Pinard has aptly described as "placenta truffé."

These structures are also designated as red infarcts, though many authors prefer to speak of them as apoplexy of the placenta. They differ markedly in structure and appearance from the other form of so-called red infarcts, and as far as we can learn, have nothing in common with them.

These conditions of the placenta have probably been noted ever

since physicians began to devote attention to the study of the afterbirth, and an immense amount of literature has gradually developed upon the subject, which, roughly speaking, may be divided into two periods, in the latter of which (from 1880), an immense number of monographs have appeared. Unfortunately, the views of the various authors have been so divergent that the immense literature has served to increase the perplexities of the student, rather than to lead to the acceptance of uniform ideas concerning the significance and mode of production of the changes under consideration.

During the past few years, we have been very much interested in the subject, and, in the hope of arriving at clearer ideas concerning it, have collected five hundred successive placentæ, all of which were carefully described in the fresh state and then hardened either *in toto* or in small pieces, and afterwards subjected to routine microscopical examination.

In the present article, it is our intention to report the results of our studies in the hope that we may thereby arrive at satisfactory conclusions concerning the significance and mode of origin of placental infarcts. But before considering our own work, we think it would be well to consider as briefly as possible the work which has been done by others upon the subject.

History.

The first reference to infarcts of the placenta, which we have been able to find in the literature, was made by Mauriceau in 1668, who designated the condition as "Schirrus of the Placenta," and considered that it might cause retardation of its delivery by making it more resistant, but he did not go into details concerning it. It is evident, however, from what he said that it was a perfectly well-known condition at that time.

During the last century, the condition was designated by a number of terms, those most frequently employed being schirrus, encephaloid and tuberculosis of the placenta. With the beginning of this century other designations were introduced, and we cannot better demonstrate the confusion which prevailed than by giving a list of some of the more important terms which were applied to it. We shall accordingly mention a number of terms by which the condition was described, and the principal authors who made

use of them. We do not, however, claim that the list is exhaustive:—

Schirrus (Mauriceau and Levret).

Atrophy (Cruveilheir).

Placentitis (Brachet, Wilde, Simpson, Hegar and Maier).

Hepatisation (Brachet and Scanzoni).

Apoplexy (Cruveilheir, Jacquemier, Gierse and Meckel and Scanzoni).

Hæmatoma (Klebs).

Phthisis (Simpson).

Fatty and Fibro-fatty Degeneration (Barnes, Robin, Charpentier and Tarnier).

Fibrin-ablagerungen,
Fibrin-anhaüfungen,
Fibrin-keile,
Fibrin-gerinnungen,
} Rokitansky, Spaeth and Wedl, Klob, Valenta, and Eberhardt.

Thrombosis (Bustamente, Slavjansky, Rohr, Martin and Delore).

Infarct (Ollivier, Rokitansky, Hoffmann, Ackermann, etc.).

Gumma (Zilles).

Necrosis (Clemenz).

Hyalin Degeneration of the Decidua (Jacobsohn).

It is apparent from this list that there was no unanimity concerning the classification of these conditions, and a similar divergence of opinion will be found concerning all other points connected with them.

The statements concerning the frequency of the affection vary quite as greatly as the terminology, and we find it variously estimated by different authors at between two and one hundred per cent. Thus:

Meyer, 1889, in 344 cases found infarcts in 2 per cent;

Spaeth and Wedl, 1855, in 2108 cases found infarcts in 3.2 per cent;

Hansen, 1890, in 300 cases found infarcts in 9.7 per cent;

Valenta, 1866, in 2471 cases found infarcts in 10.8 per cent;

Fehling, 1891, in 2008 cases found infarcts in 15½ per cent;

Rossier, 1888, in 1194 cases found infarcts in 17½ per cent;

Steffeck, 1890, in —— cases found infarcts in 50 per cent;

Delore, 1899, in several thousand cases, found infarcts in 100 per cent.

We also find a number of authors, who, at widely separated periods of time, stated that infarcts were of frequent occurrence, or even occurred in the majority of all placentæ, among whom may be mentioned Cruveilheir, Gierse, Tarnier, Clemenz, Küstner, Jacobsohn and others.

Turning to the consideration of the views concerning the etiology of the condition, we find that they are quite as diversified and contradictory as those concerning its terminology and frequency.

One of the earliest views was advanced by Cruveilheir, who designated the condition as atrophy, and believed that it resulted from the separation of the placenta from the underlying decidua, whereby the maternal vessels were lacerated and anæmia of larger or smaller areas of the placenta resulted.

One of the most important of the early theories as to the etiology of the disease was advanced by Brachet in 1823, who believed that the condition was of inflammatory origin and should be designated as placentitis, and that the patches throughout the placenta represented inflammatory exudate. Similar views were likewise held by Wilde and Simpson, and at a later period by Scanzoni and Rokitansky.

It may be remembered that Scanzoni thought that a marked similarity existed between the placental disease and pneumonia, and therefore designated certain conditions of the placenta as hepatisation. The inflammatory nature of some cases, at least, was admitted by Ollivier in his article in the Dictionnaire de Medicine in 1840. Since the time of Scanzoni, however, this view has found few adherents, and at present possesses only an historical interest.

Almost simultaneously with the inflammatory theory, it was thought by many that infarcts were the result of the organization of hemorrhagic areas. And Cruveilheir, in his article upon apoplexy of the placenta, stated that he had observed a complete series of cases, demonstrating the metamorphoses between ordinary apoplexy and the pale, white fibrous areas. This doctrine was enthusiastically championed by Jacquemier in 1839, who stated that the inflammatory theory was based upon absolutely erroneous observations; and his views were accepted in their entirety by Gierse and Meckel, Klebs, Valenta, and many others, and has not been completely forsaken even at the present time. Thus, we find that Schaeffer believes that many of the small subchordial infarcts are

the result of the organization of localized hemorrhages, and Ribemont-Dessaignes still believes that the ordinary red infarct is gradually converted into the white by a process of organization. This view, as we shall see, is not satisfactory, and was based upon the gross appearance of the lesion, rather than upon histological study.

That neither the inflammatory nor hemorrhagic theories were altogether satisfactory, even at the time of their promulgation, was shown by the fact that they were not accepted by Spaeth and Wedl, who believed that the condition was the result of the deposit of excessive amounts of fibrin from the blood, which was circulating through the placenta; and also by the statement of Klob in 1865 that none of the theories which had been advanced up to that time were satisfactory.

In the early fifties, Barnes stated that the condition in question was the result of fatty degeneration, and his views have since held almost complete sway in England and in this country.

In 1854, Robin stated that the essential feature of the affection was in a fibrosis of the chorionic villi, associated with fatty changes. Similar views were also held by Charpentier, Tarnier and others, and the accepted terminology in France at the present time is fibro-fatty degeneration of the placenta.

Hegar and Maier in 1867, stated that the condition was due to an interstitial growth in the placenta, and likened it to cirrhosis of the liver.

In 1868, Bustamente advanced the theory that the condition was essentially thrombotic in origin, and this view finds many defenders at the present day, among whom may be mentioned Rohr, Jacobsohn and Orth.

Among the more recent theories which have been more or less generally accepted, is the one which was advanced by Ackermann in 1884, according to whom the process consists essentially in a periarteritis of the fœtal vessels, with coincident coagulation necrosis of the superficial portions of the villi. As the result of the necrosis, certain substances are set free which cause coagulation of the blood in the intervillous spaces, with the consequent fusing together of larger or smaller numbers of degenerated villi by masses of fibrin. As the villous circulation becomes more and more impaired, the central portions of the villi degenerate, so that

at last one finds merely the shadows of the villi matted together by fibrin.

More or less closely related with this theory is the view of Langhans, that the condition is due merely to the excessive formation of canalized fibrin, which a few years previously he had described as one of the normal constituents of the placenta.

Ackermann's theory was first enunciated in 1882 in a dissertation by Hoffmann, one of his students, and still further elaborated in his own article in Virchow's Archiv, Band XCVI, 1884.

While we attribute to Ackermann the credit of being the first to distinctly formulate this view, it must be remembered that several other observers had noted arterial changes in the villous vessels years before him, among whom may be mentioned Robin, Maier, Tait and Ercolani, none of whom appeared to fully appreciate their significance.

In 1891, Ackermann still further modified his views by stating that he had been in error in considering periarteritis as the cause of the superficial necrosis of the villi, and that further study had enabled him to demonstrate the presence of endarteritis as well, which he was inclined to consider the real cause of the necrosis. He also believed that he had exaggerated the part played by the maternal blood, for when he wrote his first article he was not so well acquainted with the fibrinous and hyalin degeneration of necrotic cells.

His conception of the process has been more or less completely accepted by a considerable number of observers, among whom may be noted Cohn, Fehling, Wiedow, Küstner, Prinzing, Orth, Eden and others.

For several years, Ackermann's view was the prevailing one; but in 1890 its preeminence was assailed by the work of Steffeck, according to which the essential feature of the condition did not consist in primary vascular changes, but was to be found in an excessive proliferation of the decidual cells, which grew up around individual villi and groups of villi, and so interfered with their nutrition as to cause necrosis. The arterial changes he considered could not always be demonstrated, and were purely secondary when present. He believed that this method of infarct formation was not limited to the maternal portion of the placenta, where decidual tissue was abundant, but applied equally well to infarcts which

were situated in the depths of the placenta or on its fœtal surface. In such cases, he considered that the decidual cells were derived from decidual septa, whose circulation was exposed to marked danger of interruption, by which the impetus was given to the proliferation of the cells.

Steffeck was not the first observer to believe that the prime factor in the production of the lesion was to be found in the decidua, as more or less similar views had previously been expressed by Maier, Rossier, Clemenz and Küstner in some cases; while Veit believed that the primary cause of the affection was to be sought in an endometritis, which had existed before the onset of pregnancy.

A view almost identical with Steffeck's was enunciated independently by Jacobsohn in the same year. And the teachings of the former have since been accepted by a number of observers, notably Mijnlieff, Schaeffer, Ehrendorfer and von Franqué.

A certain number of observers have also thought that they could find the primary cause of the disease in changes in the maternal vessels in the decidua, which resulted in thrombosis and subsequent interference with the circulation of larger or smaller portions of the placenta. Such views were held by Rossier and Rohr, and in a modified way by Ribemont-Dessaignes.

A few observers, notably Favre, Martin and Delore, have suggested that a bacterial origin might be invoked for a certain number of cases. Favre, however, was the only one of the three to resort to cultural methods, and his results were based upon so few cases as to be without value.

The latest view as to the origin of infarcts was advanced by Eden, who accepted Ackermann's teachings in a modified way, and believed that the arterial changes in the villi were the expression of old age on the part of the placenta, and that infarcts should not be regarded as a disease, but rather as a sign of senility. Forty years previously, Druitt advanced a somewhat similar view, which was not, however, based upon microscopic study.

From the time of Cruveilheir, most observers believed that infarcts exerted no influence upon the health of the mother, and only indirectly affected the child, which began to suffer as soon as a considerable portion of the placenta was thrown out of function by infarct formation.

Gradually it began to be noted that fœtal death occurred far

more frequently when the mothers suffered from albuminuria. A little later it was discovered that the placentæ of albuminuric women contained infarcts considerably more frequently than in other conditions; and an attempt was made to demonstrate a relationship between albuminuria and infarct formation, on the one hand, and fœtal death on the other.

As far as we know, the first reference to this relationship was made by Chantreuil in 1881, who pointed out the marked fœtal mortality in albuminuric patients, but failed to mention the occurrence of infarcts in such cases.

The connection between albuminuria, infarct formation and fœtal death was first distinctly formulated by Fehling, in 1886, who reported the histories of six women with albuminuria during pregnancy, all of whom gave birth to dead children. Upon examining the placentæ, he found that five presented marked white infarctions, while the sixth contained both red and white infarcts.

In the following year, Rouhaud, in a Paris thesis, reported sixty cases of albuminuria occurring during pregnancy, and stated that 40 per cent of the placentæ from them contained red infarcts. He also stated that 40 per cent of the children were born dead in the red infarct cases, but only rarely when the placenta was normal. He therefore argued that the albuminuria caused the formation of red infarcts, and when they involved the placenta sufficiently to interfere with its circulation to a considerable extent, that the children were born dead. He did not, however, attempt to explain the connection between the two processes, and failed to give a histological description of the placental lesions.

In 1888, Cohn reported fifteen cases of nephritis occurring in pregnant women in Schroeder's clinic in Berlin, 87 per cent of whom gave birth to dead children, and upon examining the placentæ, found that only two of them were normal.

In the same year, Rossier reported from Fehling's clinic that he had observed infarcts in 17½ per cent of his cases, his observations being based upon the examination of 1174 placentæ. Among this number of cases, 54 women suffered from albuminuria during pregnancy, in 60 per cent of whom infarcts were observed. In other words, infarcts occurred three times more frequently when albuminuria was present. He believed that the excessive infarct formation in such cases was due to changes in the maternal vessels

in the decidua, but was unable to adduce convincing evidence in support of his belief.

Varnier, almost at the same time, in a long article upon eclampsia, made similar statements, but did not give the figures upon which they were based.

Wiedow, likewise, reported six cases of albuminuria during pregnancy, in all the placentæ of which infarcts were observed; but, in view of the frequency of infarct formation in non-albuminuric cases, expressed a doubt as to whether albuminuria played so important a part in their production as was generally believed.

The following year (1889) Leopold Meyer, of Copenhagen, reported his observations, which were based upon the examination of the placentæ from 1124 patients; in 1.7 per cent of which he found infarcts. When the urine contained albumin but no casts, infarcts were observed in 2.2 per cent of the cases; while when both albumin and casts were demonstrated they were noted in 6.7 per cent of the cases; that is, four times more frequently than when the urine was normal. These figures differ very markedly from those of Rossier, and the cause for the difference must probably be sought in their varying conceptions as to what constituted an infarct.

In 1890, Hansen noted the occurrence of placenta marginata 29 times in 300 cases (9.7 per cent), and believed that it exerted a marked influence upon the development of the child, as in 11 cases in which it was well marked, only one child was born whose weight and general development corresponded with the duration of pregnancy.

The following year, Cagny wrote an article upon the subject, which was based upon the examination of 2349 placentæ from Pinard's clinic in Paris, 171 of which were obtained from albuminuric women, and in one-third of these he was able to demonstrate the presence of red infarcts. He also stated that only one-third of the children from the infarcted cases presented the normal weight.

In the same year, Fehling made a second report upon the relation between albuminuria and infarct formation, and stated that infarct formation was observed in 54.9 per cent of the 91 women who suffered from albuminuria during pregnancy.

In 1892 Mijnlieff likewise referred to the subject, but did not

express himself nearly so emphatically as Fehling, Rossier or Cagny.

The latest contribution to the subject was made by Martin in 1896, who stated that he had observed infarcts in 47 per cent of the placentæ which were obtained from women suffering from albuminuria during pregnancy, and that in 67 per cent of these cases the children were either born dead or imperfectly developed.

It is accordingly apparent that the vast majority of investigators who have busied themselves with this subject, believe that a marked relation exists between albuminuria and infarct formation; and that the latter exerts an appreciable influence upon the well-being of the fœtus. But none of them adduce a satisfactory explanation for the part played by the albuminuria in their formation. And it is also evident that they do not agree among themselves concerning the subject, for certain of them, as Meyer, for example, estimate the frequency of infarct formation in albuminuric cases at only a fraction of what other investigators observe in normal cases. This difference, however, may be more apparent than real, and may be attributed to a varying conception as to what constitutes an infarct.

Pinard is a most enthusiastic advocate of this relationship, and, when I was at his clinic, daily examined the placentæ which had been born in the previous twenty-four hours; and whenever infarcts were present to any extent, immediately stated that the mother had probably suffered from albuminuria, and caused her history to be investigated in that particular.

Frequency.

Turning from the consideration of the work of others to our own investigations, we shall consider, in the first place, the frequency of infarct formation. And we may say in advance that we have observed it, to a greater or less extent, in every full-term placenta which we have examined. In a certain number of cases, however, the areas were quite small, while in others they were visible only under the microscope.

In estimating the frequency of infarcts, we have adopted the arbitrary rule of not considering surface or central infarcts which measure less than 1 cm. in diameter, and have only designated as marginal infarcts those which extend around at least one-third of the periphery of the placenta.

Applying these standards to our 500 placentæ, we found white surface or central infarcts in 243 cases (44.6 per cent) and marginal infarcts in 77 cases (15.4 per cent). In 107 other cases, a combination of marginal and central or surface infarcts was noted. Including these with the uncomplicated marginal infarcts, it is found that the latter were observed in 184 cases (36.8 per cent). In 15 cases (3 per cent) red infarcts were present. It should be noted, however, that no distinction has been made between marginal infarctions and the margo placentæ (Küstner). Upon adding together our results, we find that

Surface infarcts were observed in 223 cases, 44.6 per cent; pure marginal infarcts in 77 cases, 15.4 per cent; and red infarcts in 15 cases, 3 per cent, making a total of 315 cases, or 63 per cent.

Microscopic Appearance.

On inquiring as to the appearance and situation of the infarcts, we find that the superficial white infarct occurs most frequently, and is usually situated upon the fœtal surface of the placenta. Next in frequency are the central, fibrinous infarcts (Fibrin-keile), which are situated in the substance of the placenta, and often extend to its maternal, and less frequently to its fœtal surface.

In a still smaller number of cases, we find that larger areas of the placenta are involved in the infarct formation, which sometimes extends over one or more cotyledons. In such cases, the infarct usually extends upwards for a considerable distance from the maternal surface into the substance of the placenta, and occasionally reaches its fœtal side. The red infarcts are usually central in situation, and when they attain a considerable size extend through the entire thickness of the placenta.

Before considering the microscopic structure of infarcts in detail, we may state that we have been unable to note essential differences in structure between the marginal and other varieties of infarction, with the exception of the red infarct.

In considering the microscopic structure of infarcts, we shall study first the most fully developed variety, namely, the white, fibrinous infarct, and then take up the less developed forms until the earliest stages of infarct formation are reached.

The fibrinous infarcts, which we observe in their most fully developed form in the substance of the placenta, represent the

final stage of the process. On section through the fresh placenta, they present a dull white, somewhat fatty appearance, and are usually sharply marked off from the surrounding tissue, and on closer examination present a reticular structure.

Under the microscope they are seen to be composed entirely of fibrin, which is made up of myriads of interlacing bands, between which no trace of the original placental tissue can be discovered, and when stained by Weigert's method present the characteristic blue coloration.

In the vast majority of cases, however, this is not the form of infarct which we observe, for we usually meet with less developed varieties, which consist of a mass of fibrin, in which are embedded numbers of more or less well-preserved villi. In many instances the stroma of the villi presents an almost normal appearance, except for the presence of more or less endarteritis. The epithelium, on the other hand, is destroyed to a great extent, and only here and there do we meet with masses of syncytium scattered through the infarct.

In other cases, we find that the stroma of the villi has undergone marked changes, and presents an almost fibroid appearance, which is accompanied by the disappearance of a large part of its nuclei; while in still more advanced cases almost all the nuclei have undergone degeneration, and the stroma of the villus has become converted into a structure whose component parts can no longer be distinguished, and which takes on a homogeneous pink stain with eosin.

In still other cases, the degenerative changes have progressed still further, and the infarct consists of a mass of fibrin, through which are scattered a few pale, irregular areas, which represent all that is left of the villi—mere shadows as it were. The stage is clearly shown in Plate I, Fig. 1.

In smaller infarcts, and not infrequently in large ones as well, we do not meet with anything like so marked changes, and usually find that the stroma presents a perfectly normal appearance, excepting the arterial changes, and that the only sign of disease is to be found in the presence of a small ring of canalized tissue which stains pink with eosin, and lies just beneath the syncytium. This is identical with the tissue which Langhans first described as canalized fibrin. Here and there certain of the villi have lost the greater

part of their syncytial covering, and have become fused together by canalized fibrin, but are not matted together by fibrin

Occasionally, we note that the infarct is composed not only of fibrin and more or less degenerated villi, but that scattered through it are irregularly shaped masses of large cells with round vesicular nuclei, which stain tolerably intensely, and may present various degrees of degeneration. Such areas are usually spoken of as decidual islands, and are supposed to represent sections through decidual septa.

In considering the structure of red infarcts, we must differentiate, as we pointed out in the beginning of the article, between the sharply circumscribed, more or less circular, bright or dark-red infarcts, and the larger, more irregularly shaped, brick-colored masses, which often extend through the entire thickness of the placenta. To the former the term apoplexy is often applied, and when they are present in any number, the condition is designated by the French as placenta truffé. The latter, on the other hand, are paler, and ofttimes of a dull pink color, and on section are roughly granular, and do not present the homogeneous appearance of the apoplectic masses.

We are not in a position to make definite statements concerning the dark, round infarcts (apoplexy), as we have had occasion to examine them in only a few instances; but we believe that they differ essentially from the other forms of infarcts and should not be considered among them.

The large pink infarcts, on the other hand, are closely related to the ordinary varieties of white infarcts, and differ from them only in the fact that larger or smaller numbers of red blood-corpuscles are enclosed in the meshes of the fibrin network by which the degenerated villi are bound together.

In a small number of cases, we meet with large structures, which, in fresh specimens, more or less resemble large white central infarcts, but which, on closer examination, present a more striated appearance. Under the microscope we find that they are totally lacking in fibrin, and are made up of large numbers of completely degenerated villi which are very closely packed together, and between which we can discover no trace of either blood or fibrin. In most of the villi composing these masses, the degeneration is very marked, and we see only the outlines of villi, through which are scattered large quantities of nuclear debris.

These structures were designated by Eden as non-fibrinous infarcts, and according to him result from the shutting off of a certain number of maternal vessels in the decidua, by which the blood supply to the intervillous spaces in the corresponding portions of the placenta is interfered with. As these intervillous spaces are no longer filled with blood, they collapse, and the villi become closely packed together by the pressure of blood in the surrounding portions of the placenta, after which they degenerate.

We have not infrequently observed such structures, but as yet are unable to express a definite opinion as to the correctness of Eden's explanation concerning their production.

Occasionally one observes in the centre of infarcts, especially in the large pink variety, cavities filled with a thick grumous material, which in fresh specimens resembles pus; and it was the presence of such cavities which led the earlier observers to believe that placentitis played so important a part in the production. On microscopic examination, however, we find that the contents of the cavities is not pus, but is made up of cellular debris, and we believe that they are analogous to the areas of softening which are occasionally observed in ordinary thrombi.

When the infarcts contain masses of " decidual " tissue, one not infrequently notes that certain of them contain cavities which are filled with a more or less clear fluid. Upon closer examination, it is apparent that this was produced by the degeneration and breaking down of certain of the cells of the mass, and they will be considered more in detail when we take up the question of the relation of infarcts to the formation of placental cysts.

Etiology.

Careful microscopical examination of a number of sections from each of our five hundred placentæ has led us to believe that in the great majority of cases the main factor in the production of infarcts is to be found in arterial changes in the villous vessels. These are usually manifested as an endarteritis of an obliterative character, with which periarteritis is not infrequently associated. The changes are particularly well marked in the vessels of the medium-sized villi, but are less prominent in the large villous stems and the terminal branches of the villi.

The degree to which the lumen of the vessels is encroached upon differs markedly; in some cases there is only a slight bulging of the intima, while in others the lumen is almost obliterated.

The arterial changes are identical with those observed in obliterating endarteritis in other portions of the body, and are in no way related to those which Merttens has recenly described as occurring in villi after the death of the fœtus.

As the result of our studies we have no hesitancy in confirming the statements of Ackermann, Eden and others concerning the frequency with which these changes occur and the part which they play in the production of infarcts.

Figure 1, Plate II, gives an excellent idea of the arterial changes, and demonstrates at the same time certain of their effects, to which we shall refer later.

As the result of the interference with the arterial supply of the villi, we soon observe changes in the portion of the stroma which lies just beneath the syncytium; in other words, where the Zellschicht was observed in the earlier months of pregnancy. On attentive examination in suitable cases, we notice that the nuclei of the cells in question become somewhat larger, more irregular in shape, and gradually lose their ability to stain with the ordinary reagents. In other words, they undergo coagulation necrosis. A little later, we notice that the protoplasm of the cells appears less well differentiated and adjacent cells fuse together, while in the intercellular spaces between them a tissue gradually makes its appearance, which is analogous to Langhan's canalized fibrin.

In the earlier stages of the process the syncytium is not affected, and does not appear to undergo marked changes until a layer of canalized fibrin of considerable thickness has been formed beneath it. Such changes are well shown in Figs. 1 and 2, Plate II.

In Fig. 1, Plate II, we also notice that the entire stroma of the villus has taken on a somewhat fibroid appearance, contains fewer nuclei and more intercellular substance, and stains more intensely pink with eosin than is usual. Robin and the investigators who followed him, probably observed the same condition, and designated it as "fibrosis."

As we have already stated, the syncytium does not become involved in the degenerative process until a later period, and it may well be asked, if the changes in question are the result of interfer-

ence with the villous circulation, why the first changes are observed in the tissue directly beneath the syncytium, instead of in the syncytium itself. We believe that the answer to this question is to be found in the fact that the syncytium, lying in direct contact with the maternal blood, practically serves as an endothelium for the intervillous spaces, and probably plays an important part in preparing it for transmission to the fœtal vessels. It is probably nourished in large part by the maternal blood, so that it will not begin to degenerate until the condition of the tissue beneath it renders its further preservation unnecessary.

Infarct formation does not occur uniformly over the entire placenta, but is limited to larger or smaller groups of villi, so that the beginning of the process is nearly always sharply localized. Gradually, however, after a well-defined layer of canalized fibrin has been developed beneath the syncytium, we note the appearance of changes in the syncytium itself, which undergoes coagulation necrosis, and is also converted into canalized fibrin. This, however, does not usually occur over the entire periphery of the villus, but only in localized areas. As soon as the syncytium of several adjacent villi has been replaced by canalized fibrin, the degenerated areas immediately fuse together, and we find several small villous branches united by a band of canalized fibrin, and this represents the earliest stage of infarct formation.

As the process goes on, larger and larger areas of syncytium degenerate, so that eventually we have a number of villi, a considerable portion of whose surface is covered by canalized fibrin, but which are separated one from another by the maternal blood in the intervillous spaces. In a short time, fibrin ferment, or some analogous substance, is set free from the degenerated cells, and the maternal blood, which lies between the degenerated villi, begins to coagulate. (Fig. 2, Plate I, gives a very good idea of the process.) By the coagulation of the contents of the intervillous spaces, a number of degenerated villi become firmly fused together by a mass of fibrin, and a typical infarct is produced.

In the earlier periods of infarct formation, the degenerative changes are limited to the periphery of the villi, and the great bulk of their stroma remains unchanged. As the process goes on, however, the arterial changes become more marked, and the stroma more and more degenerated, until in well-marked cases it is repre-

sented by a mass of degenerated tissue in which individual cells cannot be distinguished. This change, we also consider, is the result of coagulation necrosis, and we believe that eventually the entire stroma will be converted into canalized fibrin, which later on will be indistinguishable from the fibrin formed by the coagulation of the maternal blood, so that finally a mass of fibrin is formed, which is derived partly from the degenerated villi and partly from the maternal blood; and such structures represent the fibrinous infarcts to which we have already referred.

In a certain number of instances, especially in infarcts which are situated at or near the margin, or near the maternal surface of the placenta, the method of origin which we have just described does not appear to offer a satisfactory explanation for the phenomena observed. For in some cases, we also find so-called decidual cells taking part in the formation of the infarct. Fig. 2, Plate II illustrates this condition, and in it we see a villus abutting upon the serotina, with its superficial portions converted into canalized fibrin, but about whose base are large numbers of epithelioid cells, which are continuous with those of the decidua serotina, and which present various stages of degeneration.

At first glance, such a specimen apparently substantiates Steffeck's contention concerning the decidual origin of infarcts; and this is rendered still more striking by the consideration of Plate III in which we find a large area of decidua-like cells projecting from the decidua into the substance of the placenta and undergoing degenerative changes, around which are grouped a certain number of degenerated villi. This area is made up of comparatively large cells, which are distinctly epithelioid in appearance. Many of the cells stain clearly and distinctly, while in others the nuclei have lost their vesicular appearance and stain feebly; in others the nuclei have entirely disappeared, and all trace of structure has disappeared from their protoplasm, and in still other places, several degenerated cells have fused together, forming a mass of fibrinous material.

At first glance, one naturally considers that the structure in question is simply a section through a decidual septum, and this supposition is strengthened when one finds that it is continuous with the decidua serotina. But careful study shows that there is a marked difference between the cells of the so-called septum and those situated in the deeper portions of the serotina.

No doubt Steffeck saw similar specimens, and concluded from them that the initial changes in infarct formation originated in decidual (maternal) tissue.

The question we now have to consider is, whether he interpreted such specimens correctly, and for our part we do not believe that he did; but consider that the great majority of structures which he considered as decidual septa and islands were not such, but were composed of Zellschicht cells (fœtal ectoderm).

Nowhere in Steffeck's work, nor in the work of those who substantiate his statements, do we find mention made of the fact that the decidua serotina is not entirely of maternal origin, but contains in its upper layers large numbers of cells which are derived from the fœtal ectoderm.

Nitabuch was the first observer to direct attention to this point, when she demonstrated the presence of a band of canalized fibrin in the upper part of the decidua serotina, and showed distinctly that there was a marked difference between the tissue which lay above and below it, that on the maternal side of the fibrinous layer being decidual in origin, while that on its fœtal side was derived from the fœtal Zellschicht.

More or less similar views were soon expressed by Rohr, which have since been abundantly confirmed by the work of Kastchencko, Minot, Rheinstein-Mogoliwa and Marchand, and we have been able to confirm their observations in all of the early placentæ which we have studied.

The work of Nitabuch demonstrated with tolerable certainty that the fibrinous layer in the decidua serotina was probably produced by the degeneration of Zellschicht cells; and it is more than probable that a large part of the tissue, which thus far has been designated as decidual, whether occurring in the form of decidual septa or islands, or as a layer of cells on the maternal surface of the chorionic membrane, is of similar origin and corresponds to Langhans's Zellschicht.

The same idea was expressed in a modified way by Eberhardt, who, after carefully studying the formation of canalized fibrin in Langhans' laboratory, concluded that it was always derived from Zellschicht cells, wherever it was observed in the placenta.

The probability that a large part of the tissues, which have thus far been considered as decidual, are really fœtal in origin, has prac-

tically been converted into a certainty by the recent work of Peters, who has carefully described the earliest human ovum which has thus far been observed. In his specimen, the ovum, instead of being attached to the surface of the decidua serotina, as had been previously taught, was found embedded in the serotina beneath the uterine epithelium. And he accounts for this by supposing that the ovum had become implanted upon a portion of mucosa which was denuded of its epithelium, and then burrowed down into the stroma of the endometrium.

In the excellent microscopic pictures which accompany his article, one finds that the entire ovum is surrounded by many layers of epithelial cells, which he has designated as trophoblast, the majority of which are sharply marked off as individual cells, though a certain number of them are syncytial in appearance. Scattered through this mass of cells are a large number of blood spaces, which have resulted from the opening up of maternal capillaries by the growing trophoblast, and which we must consider as the earliest stages in the formation of the intervillous spaces. Surrounding the ovum are a number of rudimentary villi, with a distinct connective-tissue stroma, each of which is surrounded by many layers of the trophoblastic cells.

Nowhere in his specimens does one observe decidual septa growing up between these cells, and it appears highly probable to us that certain bands of the trophoblastic cells may persist until a later period, when they will appear as the structures which we now designate as decidual septa and islands, and even as Winckler's "Schluss-platte."

Careful study of the so-called decidual islands in the full-term placenta fails, as a rule, to reveal the presence of vessels, which are likewise absent from the layer of "epithelioid" cells on the fœtal surface of the chorion, which were considered by Winckler and others as decidual in origin. Owing to the absence of vessels, such tissue is extremely prone to degeneration, and we believe that the initial stage in many cases of infarct formation is afforded by their degeneration.

Eberhardt has offered a very plausible objection to Steffeck's theory that in many cases the impetus to the formation of infarcts is first given by the blood supply of a decidual septum being interfered with, by inquiring why that should make any difference, if

the septa be of maternal origin, so long as they are surrounded by the maternal blood in the intervillous spaces. And he pertinently asks why they should not be nourished by it quite as well as by maternal blood contained in blood-vessels.

We are inclined to accept Eberhardt's views, and, as indicated above, believe that the great majority of such structures are derived from the fœtal ectoderm.

If this should prove to be the case, the primary change in the production of infarcts will accordingly be nearly always found in fœtal tissues, most frequently in the villi, but in a certain number of cases, in the above-mentioned masses of fœtal ectoderm (decidual islands and septa). This supposition appears to us to receive additional confirmation when we consider that the most frequent situation for small infarctions is on the maternal surface of the chorionic membrane, as we believe that the epithelioid cells which are found in that situation present only a superficial resemblance to decidual cells, and are undoubtedly of fœtal origin.

If these views be correct, the vast majority of infarcts, wherever situated, are fœtal in origin, and their only maternal constituent is the fibrin, which has resulted from the coagulation of the blood in the intervillous spaces.

While we believe that the views just expressed are correct in the vast majority of cases, we do not wish to be understood as absolutely denying the possibility of the process originating in some cases as Steffeck has suggested, but we do not consider that the evidence which has thus far been adduced in support of his theory is satisfactory or convincing.

Turning to the consideration of red infarcts, we shall first consider the structure of the large pink infarction, and, as far as our experience extends, we can see no marked microscopic difference between them and the usual white infarcts, except in the fact that the blood in the intervillous spaces has not become completely converted into fibrin; and we must, therefore, attribute their pink color to the presence of unchanged red blood cells in the meshes of the fibrin network. And we believe that the most satisfactory explanation for the occurrence of such structures is to be sought in a more rapid formation of the infarct, with consequent imperfect coagulation of the blood between the individual villi composing it.

We have not had an opportunity to examine a sufficient number

of the round, dark red infarcts, the so-called apoplexy of the placenta, to justify us in expressing definite views concerning their etiology. Numerous theories have been advanced to explain their production, but none of them appear to us to be entirely satisfactory.

Bustamente suggested that they were probably due to the occurrence of hemorrhage into an area of beginning infarct formation, so that the effused blood was poured out into spaces bounded by degenerated and fused together villi, instead of into the ordinary intervillous spaces. This view was also adopted by Charpentier, and presents a certain degree of plausibility.

We cannot, however, speak of such changes as hemorrhage into the placenta, for the reason that the intervillous spaces are, in themselves, blood-vessels; and we are hardly justified in speaking of hemorrhage into blood-vessels. This view has been especially elaborated by Schilling, who believes in some cases, that we have to deal with a thrombosis which originates in the maternal vessels of the decidua, and then gradually spreads into the intervillous spaces, involving a larger or smaller portion of the placenta.

Concerning the non-fibrinous infarcts to which we have already alluded, we can only say that the microscopic pictures in our specimens correspond exactly to those described by Eden; and while we can suggest no more satisfactory explanation for their production than he has advanced, we are not prepared to advocate its acceptance.

From the time of Rokitansky, a certain number of observers have considered that some connection existed between infarct formation and syphilis, such views being held by Zilles, Fuoss, Prinzing, Orth and others. We, however, have not found that infarct formation was observed more frequently in syphilitic than in normal placentæ, and in view of their marked frequency in non-syphilitic cases, we believe that we are justified in denying the existence of any relation between them.

Several observers, notably Favre, Martin and Delore, have suggested that the presence of bacteria in the intervillous spaces may so damage the villous epithelium as to lead to its death, and thus afford the starting point for infarct formation. None of them, however, has advanced satisfactory proof of their presence, and Favre is the only investigator who has attempted to verify his theory by bacteriological research.

We have examined some twenty placentæ bacteriologically, and have found that they were always sterile when cultures were taken from the centre of the organ with proper precautions. As the vast majority of these placentæ contained infarctions, we believe that we are fully justified in denying their bacterial origin.

The part played by albuminuria in the production of infarctions, on the other hand, is not so readily disposed of; and from the statements of the various authors which we have already adduced, there appears to be but little doubt that albuminuria on the part of the mother leads in many instances to a marked increase in the number of infarctions. In our own cases, we have noticed a similar relationship, and can assert that the infarcts are usually larger and more abundantly scattered through the placenta, when albuminuria is present, and are more frequently of the red variety than under other circumstances.

In the cases of albuminuria in which the symptoms were so grave as to necessitate the induction of premature labor, we have almost universally found the placenta studded with considerable numbers of large white or pink infarcts, and in the majority of such cases the children have either been born dead or have weighed less than normal.

An interesting fact in this connection is that we have been unable to ascertain that there is a marked increase in the number and size of infarctions in the placentæ of eclamptic women. The explanation for this is probably to be found in the fact that eclampsia is usually an acute affection, while the cases of albuminuria have lasted a longer period.

Exactly why the number of infarctions is increased in albuminuria we are unable to state, and it is a question whether the deleterious effects upon the fœtus are due to the presence of the infarctions or to the conditions of the maternal blood. It appears, however, that the fœtal changes can be attributed to the former only when they are so large or abundant as to materially interfere with the placental circulation.

We believe with Eden that the presence of infarctions of moderate size cannot be regarded as a disease, but rather as a sign of senility of the placenta, analogous to the changes which are observed in the villi of the chorion læve at an earlier period of pregnancy. The infarct formation, however, which we observe in cases

of marked albuminuria, cannot be so considered, and under such circumstances we believe that we have to deal with a disease, which may exert a marked influence on the well-being of the fœtus.

It is not infrequent to find calcareous changes occurring in infarcts, though the deposits rarely attain a large size, no matter how abundant they may be.

Nearly all observers, who have busied themselves with the study of cysts upon the fœtal surface of the placenta, have pointed out that infarcts could usually be found at some point in their walls, and many of them are inclined to believe that the cystic structures resulted in some way from their degeneration. These views are well reviewed in Ehrendorfer's article upon cysts of the placenta, to which we would refer those who are especially interested in the subject.

Very recently Peiser has pointed out, in his case at least, that the placental cyst was the result of the degeneration and liquefaction of Zellschicht cells of the chorionic membrane, and is inclined to consider that there is no direct connection between the cyst formation and placental infarcts; but believes that the two processes merely represent the two extremes of the same process; and we feel that his conclusions are probably correct, especially in view of our observations, upon the formation of cystic structures in infarcts which contain so-called decidual elements.

Conclusions.

I. Infarcts measuring at least 1 cm. in diameter were observed in 315 out of 500 conservative placentæ (63 per cent).

II. Smaller infarcts, many just visible to the naked eye, were observed in the great majority of placentæ, while microscopic examination revealed early stages of infarct formation in every full-term placenta which we examined.

III. The primary cause of infarct formation in the great majority of cases is to be found in an endarteritis of the vessels of the chorionic villi.

IV. The primary result of the endarteritis is coagulation necrosis of portions of the villi just beneath the syncytium, with subsequent formation of canalized fibrin.

As the process becomes more marked, the syncytium likewise degenerates, and is converted into canalized fibrin, which is

followed by the coagulation of the blood in the intervillous spaces, which results in the matting together of larger or smaller groups of villi by masses of fibrin. Later the entire stroma of the villi degenerates, so that eventually the infarct consists entirely of a network of fibrin.

V. The part played by the decidua in the production of infarcts has been greatly overestimated by many observers.

It is more than probable, in many cases at least, that the tissue which they designate as decidual, is really fœtal ectoderm.

VI. Moderate degrees of infarct formation are not pathological and exert no influence upon the mother or fœtus, and are to be regarded as a sign of senility of the placenta, analogous to the changes which take place in the villi of the chorion læve at an earlier period.

VII. Marked infarct formation is not infrequently observed, and often results in the death or imperfect development of the fœtus. It is usually associated with albuminuria on the part of the mother, though at present we cannot account satisfactorily for the relationship between them.

VIII. Infarct formation is not particularly marked in cases of eclampsia, being usually observed only in those cases which were preceded by marked albuminuric symptoms.

IX. There is no evidence in favor of the bacterial origin of infarcts.

LITERATURE.

1. Ackermann. Der weisse Infarct der Placenta. Archiv f. path. Anat. [etc.], Berl., Bd. XCVI, S. 439-452, 1884.
2. Ackermann. Zur normalen u. path. Anat. der menschl. Placenta. Festschr. Rudolf Virchow, Berlin, S. 585-616, 1891.
3. Barnes. A Further Account of Fatty Degeneration of the Placenta. Med.-Chir. Tr., London, vol. XXXVI, pp. 143-168, 1853.
4. Brachet. Des maladies du placenta et leur influence sur la vie du fœtus. J. gén. de méd., chir. et pharm., Paris, vol. CII, pp. 10-60, 1828.
5. Bustamente. Étude sur le Placenta. (Anatomie, Physiologie, Pathologie), Paris, 1868.
6. Cagny. Hémorrhagies placentaires de l'albuminurie. Thèse de Paris, 1891.

7. Chantreuil. Hémorrhagies utérines et placentaires liées a l'albuminurie. Leçons faites a l'hôpital des clinques, pp. 55-61, 1881.
8. Charpentier. Des maladies du placenta et des membranes. Paris, 1869, pp. 6-55.
9. Clemenz. Anatomische und kritische Untersuchungen über sog. weissen Infarct der Placenta und über den sog. weissen Deciduaring. D. I. Dorpat, 1889.
10. Cohn. Ueber das Absterben des Fœtus bei Nephritis der Mutter. Zeit. f. Geburtsh. u. Gynaek., Stuttgart, Bd. XIV, S. 587-615, 1888.
11. Cruveilheir. Maladies du Placenta. Anat. path. du corps humain. T. I., Liv. XVI, 1829-1835.
12. Delore. Placenta normal et placenta thrombosé. Obstétrique. Paris, IV, pp. 1-27, 1889.
13. Druitt. On Degeneration of the Placenta at the End of Pregnancy. Lancet, 1853.
14. Eberhardt. Ueber Gerinnungen in der Placenta. D. I., Bern, 1891.
15. Eden. A Study of the Human Placenta, Physiological and Pathological. J. Path. and Bacteriol., Edinburgh and London, vol. IV, pp. 265-282, 1897.
16. Ehrendorfer. Ueber Cysten und cystoide Bildungen der menschlichen Nachgeburt. Wien, 1893. (Der weisse Infarct der Placenta und sein Verhältniss zur Cystenbildung, pp. 34-60).
17. Ercolani. Della malattie della placenta. Bologna, 1871.
18. Favre. Ueber den weissen Infarct der menschlichen Placenta. Archiv f. path. Anat. [etc.], Berlin, Bd. CXX, S. 460-476, 1890.
19. Fehling. Ueber habituelles Absterben der Frucht bei Nierenerkrankungen der Mutter. Archiv f. Gynaek., Bd. XXVII, S. 300-307, 1886.
20. Fehling. Weitere Beiträge zur klin. Bedeutung der Nephritis in der Schwangerschaft. Archiv f. Gynaek., Berlin, Bd. XXXIX, S. 468-483, 1891.
21. von Franqué. Anat. und klin. Beobachtungen über Placentarerkrankungen. Zeit. f. Geburtsh. u. Gynäk., Stuttgart, Bd. XXVIII, S. 293-384, 1894. (IV weissen Infarct, pp. 330-345.)

22. Fuoss. Beiträge zur pathologischen Anatomie der Placentarveränderungen bei Syphilis und Nephritis. D. I. Tübingen, 1888.
23. Gierse and Meckel. Die Krankheiten der Placenta (Blutergüsse) Verhandl. d. Gesellsch. f. Geburtsh. in Berlin, II Jahrg., S. 141-161, 1847.
24. Hansen. Placenta marginata und schlechte Entwickelung der Frucht, Hosp.-Tid., Kjbenh., 1890, 3 R., Bd. 8, S. 777-788. Referat Jahresb. ü. d. Fortschr. a. d. Geb. d. Geburts. u. Gynaek., 1890, S. 133.
25. Hegar and Maier. Die interstitielle Placentitis und ihr Einfluss auf Schwangerschaft und Geburt. Archiv f. path. Anat. [etc.], Berlin, Bd. XXXVIII, S. 387-399, 1867.
26. Hoffmann. Untersuchungen über den weissen Infarct der Placenta. D. I. Halle, 1882.
27. Jacobsohn. Untersuchungen über den weissen Infarct der Placenta. Zeit. f. Geburtsh. u. Gynaek., Stuttgart, S. 237-268, 1890.
28. Jacquemier. Recherches d'anat. de physiol. et de path. sur l'utérus humain pendant la gestation et sur l'apoplexie utéro-placentaire, etc. Arch. Gén. de Méd., Paris, 3e Ser., T. V., p. 321, 1839.
29. Jacquemier. Des maladies de l'œuf. Manuel des Accouchments, I, pp. 407-420, 1846.
30. Kastschenko. Das menschliche Chorion-epithel. und dessen Rolle bei der Histogenese der Placenta. Arch. f. Anat. u. Physiol., Leipzig, Anat. Abth., 1885.
31. Klebs. Haematom der Placenta. Monatsch. f. Geburtsh. u. Frauenkr., Berlin, Bd. XXVI, S. 272-275, 1865.
32. Klob. Fibrinanhaüfungen im Gewebe der Placenta, Path. Anat. der weibl. Sexualorgane. Wien, 1865, p. 555.
33. Küstner. Weissner Infarct der Placenta. Müller's Handbuch der Geb., II, 606-615, 1889.
34. Langhans. Untersuchungen über die menschliche Placenta. Arch. f. Anat. u. Entwicklungsgesch., Leipzig, 1877, S. 188-276.
35. Langhans. Ueber die Zellschicht des menschlichen Chorions. Beiträge zur Anat. und Embryologie. (Henle's Festgabe) Bonn, 1882.

36. Levret. De l'arrière-faix. L'art des accouchements, II Ed., p. 446, 1761.
37. Maier. Ueber Bindegewebsentwickelung in der Placenta. Archiv f. path. Anat. [etc.], Berlin, Bd. XLV, S. 305-326.
38. Marchand. Ueber den Bau der Blasenmole. Ztschr. f. Geburtsh. u. Gynaek., Stuttgart, Bd. XXXII, S. 405-472, 1895.
39. Martin. De l'influence des altérations du placenta sur le développment du fœtus. Thèse de Paris, 1896.
40. Mauriceau. Traité des femmes grosses. 6th Ed., vol. I, 252, 1721.
41. Merttens. Beiträge zur normalen und pathologischen Anatomie der menschlichen Placenta. Ztschr. f. Geburtsh. u. Gynaek., Stuttgart, Bd. XXX, S. 1-98, 1894.
42. Meyer. Zur Lehre von der Albuminurie in der Schwangerschaft und bei der Geburt. Ztschr. f. Geburtsh. u. Gynaek., Stuttgart, Bd. XVI, S. 215-268, 1889.
43. Mijnlieff. Einige Betrachtungen über Albuminurie und Nephritis Gravidarum in Zusammenhang mit dem intrauterinen Absterben der Frucht. Samml. klin. Votr., Leipzig, N. F., No. 56, S. 523-572, 1892.
44. Minot. The Placenta. Buck's Reference Hand-book of the Medical Sciences, V, 692-99, 1887.
45. Nitabuch. Beiträge zur Kenntniss der menschlichen Placenta. D. I. Bern, 1887.
46. Ollivier. Des altérations morbides de l'œuf humain. Dict. de méd., Paris, vol. XXI, pp. 547-560, 1840.
47. Orth. Infarct der Placenta. Lehrbuch der spec. path. Anatomie, vol. II, pp. 603-607, 1893.
48. Peiser. Beiträge zur Pathologie der Placenta. Monatschr. f. Geburtsh. u. Gynaek., Berlin, Bd. X, pp. 613-626, 1899.
49. Peters. Ueber die Einbettung des menschlichen Eies. Wien, 1899.
50. Prinzing. Beiträge zur pathologischen Anatomie der Placenta. D. I. München, 1889.
51. Reinstein-Mugilowa. Ueber die Betheiligung der Zellschicht des Chorion an der Bildung der Serotina und Reflexa. Archiv f. path. Anat. [etc.], Berlin, Bd. CXXIV, S. 422-429, 1891.

52. Ribemont-Dessaignes et Lepage. Placenta albuminurique. Précis d'obst., pp. 438-445, 1894.
53. Robin. Note sur les altérations du placenta. Arch. Gén. de Méd., Par., T. I., p. 705, 1854.
54. Rohr. Die Beziehungen der mütterlichen Gefässe zu den intervillösen Raümen der reifen Placenta, speciell zur Thrombose derselben ("weisser Infarct"). D. I. Bern, 1889.
55. Rokitansky. Entzündung und Infarct der Placenta. Lehrbuch der path. Anatomie, III, 545-546, 1861.
56. Rossier. Klinische und histologische Untersuchungen über die Infarct der Placenta. Archiv f. Gynaek., Berlin, XXXIII, S. 400-412, 1888.
57. Rouhaud. Lesions du Placenta dans l'albuminurie. Thèse de Paris, 1887.
58. Scanzoni. Blutergüsse in das Parenchym der Placenta, pp. 411-416. Also, Die Entzündung der Placenta, pp. 416-421. Lehrbuch der Geburtshilfe, II, Auf. 1853.
59. Schaeffer. Ueber die Placentar-Verhältnisse, in Zur Pathologie des Foetus, die Königliche Universitäts Frauenklinik in München, 1884-1890, Leipzig, 1892, 479-654.
60. Schilling. Beitrag zur Kenntniss der hämorrhagischen Laesionen der Placenta. D. I. Basel, 1895.
61. Simpson. Pathological observations on the diseases of the Placenta. Edinb. M. J., vol. XLV, p. 266, 1836.
62. Simpson. Placental phthisis or apnœa as an intra-uterine cause of death among premature children. Edinb. M. J., Feb., 1845, p. 119.
63. Slavjansky. Zur Lehre von den Erkrankungen der Placenta (Thrombosis sinuum placentæ). Archiv f. Gynaek., Berlin, V, pp. 360-366, 1873.
64. Spaeth and Wedl. Zur Lehre über die Anomalien der peripheren Eitheile. Chiari, Spaeth, Braun Klinik der Geb. and Gyn., 1855, 98-102.
65. Steffeck. Der weisse Infarkt der Placenta. Hofmeier's die Placenta, Wiesbaden, 1890, pp. 91-116.
66. Tait. Note on Diseased Placenta. Tr. Obst. Soc., London, vol. XVII, pp. 326-329, 1876.

67. Tarnier. Dégénérescence fibro-graisseuse des villosités choriales. Traité de l'art des Accouchements, II, 329-333, 1886.
68. Valenta. Geburtshilfliche Studien. IV Ein Beitrag zur Pathologie der Nebeneitheile. Monatschr. f. Geburtsk. u. Frauenkr., Berlin, Bd., XXVIII, p. 387, 1866.
69. Varnier. Albuminurie et Eclampsie. Rev. prat. d'obst. et d'hyg. de l'enf., Paris, July, Sept., Oct. and Nov., 1888.
70. Veit. Endometritis in der Schwangerschaft (weisser Infarct). Müller's Handbuch der Geb. II, p. 10, 1889.
71. Wiedow. Ueber den Zusammenhang zwischen Albuminurie und Placentarerkrankung. Ztschr. f. Geburtsh. u. Gynäk., Bd. XIV, S. 387-404, 1888.
72. Wilde. De cognoscendis et curandis placentæ morbis. Berlin, 1833. Referat. Arch. gén. de Méd., Paris, 2e Ser., VI, p. 275.
73. Zilles. Studien über die Erkrankungen der Placenta und der Nabelschnur bedingt durch Syphilis. Tübingen, 1885.

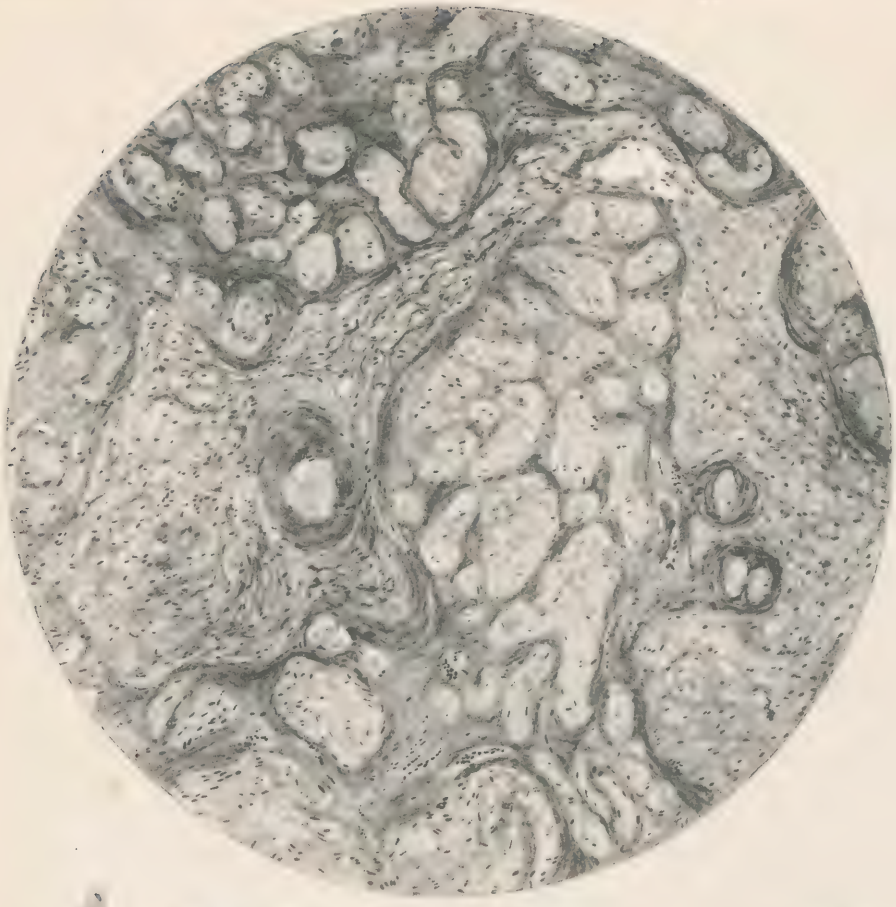


Fig. 1.

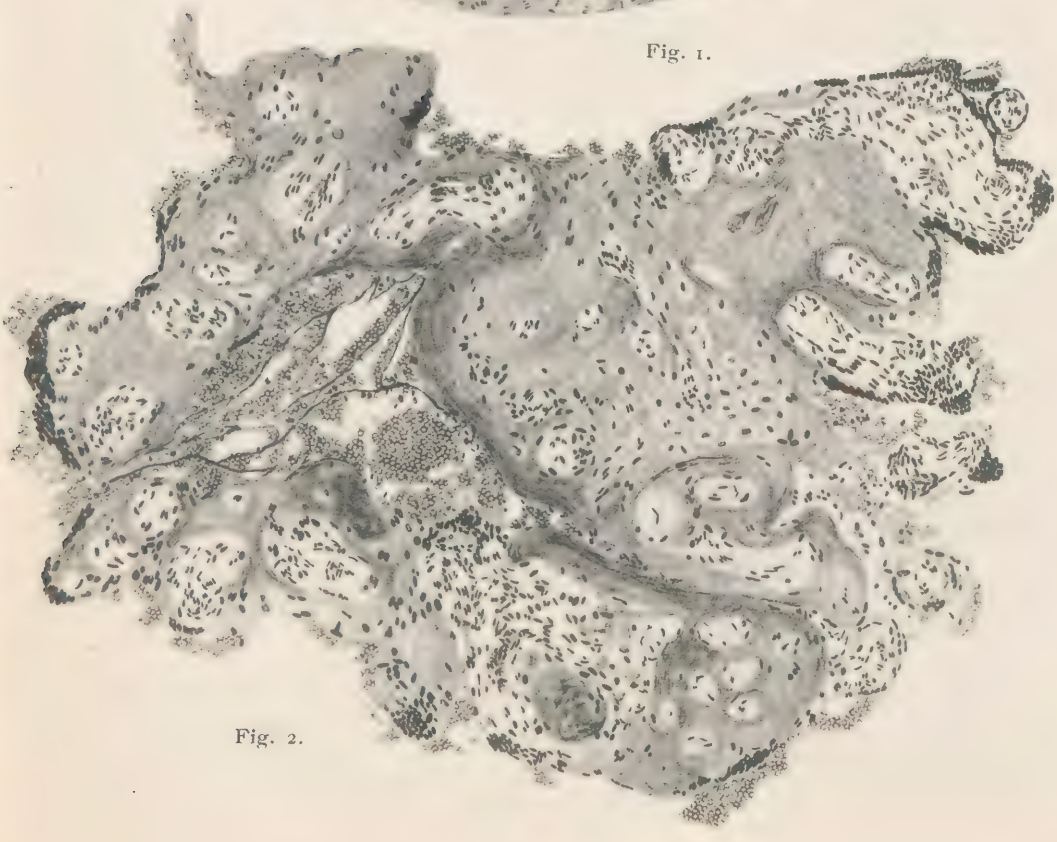


Fig. 2.

THE HELIOTYPE PRINTING CO., BOSTON.

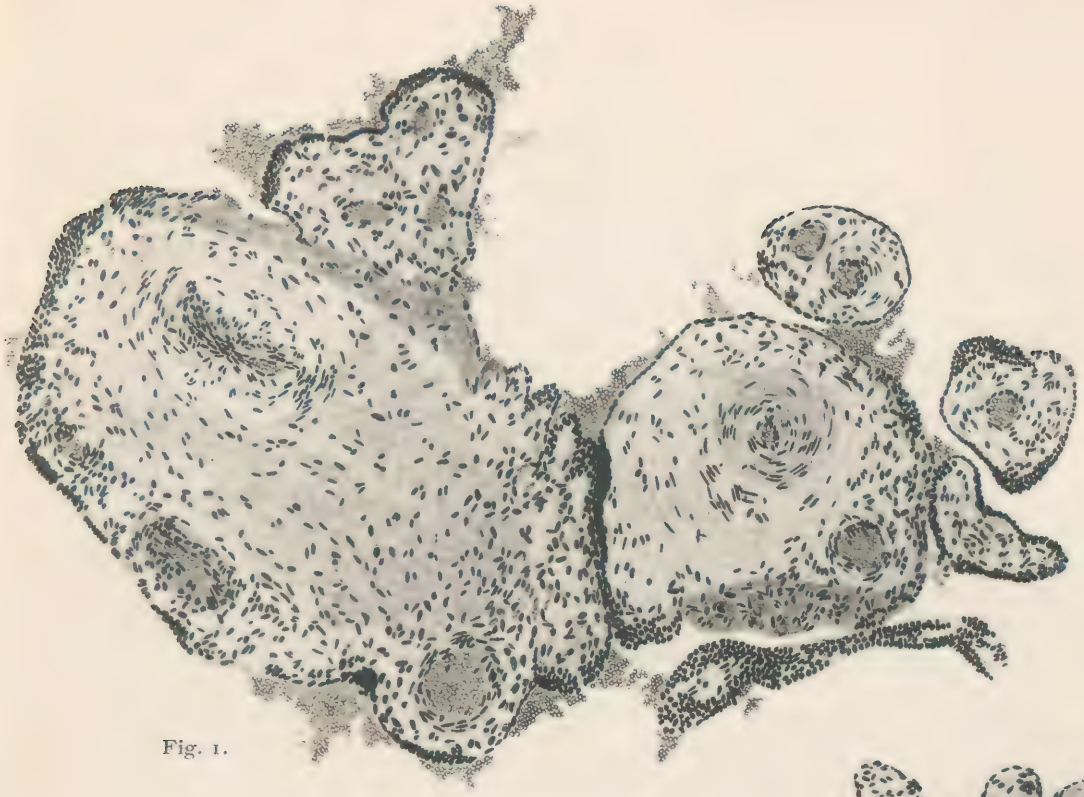
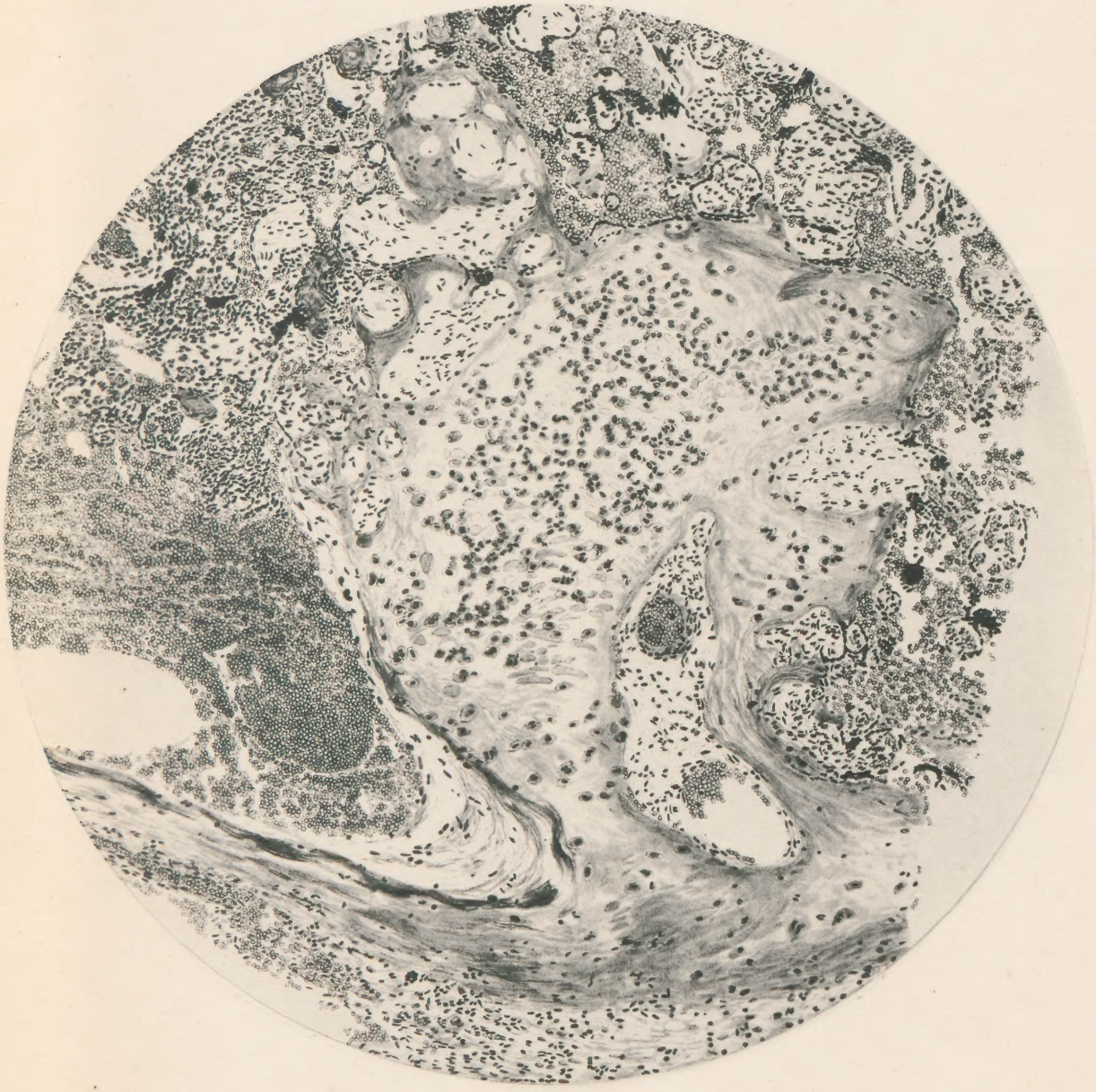


Fig. 1.

Fig. 2.

THE HELIOTYPE PRINTING CO., BOSTON.



THE HELIOTYPE PRINTING CO., BOSTON.